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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,275	10/08/2003	Hans Jochen Lang	DEAV1996/F140US	6888
5487 7590 07/17/2007 ROSS J. OEHLER SANOFI-AVENTIS U.S. LLC 1041 ROUTE 202-206 MAIL CODE: D303A BRIDGEWATER, NJ 08807			EXAMINER WILLIAMS, LEONARD M	
			ART UNIT 1617	PAPER NUMBER
			NOTIFICATION DATE 07/17/2007	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/680,275

Applicant(s)

LANG ET AL.

Examiner

Leonard M. Williams

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17, 18 and 20-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17, 18 and 20-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☒ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>01/03/05, 10/08/03</u> . | 6) ☐ Other: _____ |

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Detailed Action

Election/Restrictions

The response to the Election Restriction received 04/30/2007 electing the species 4-isopropyl-3-methylsulfonylbenzoylguanidine has been entered. Claims 17-18 and 20-44 are readable on the elected species. Claims 17-18 and 20-44 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18 and 20-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating raised blood lipid levels, does not reasonably provide enablement for preventing raised blood lipid levels. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547

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the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a method of treating or preventing raised blood lipid levels by administration of a medicament comprising at least one Na/H exchange inhibitor.

(2) Breadth of the Claims:

The instant claims embrace preventing or treating raised blood lipid levels by administration of a medicament comprising at least one Na/H exchange inhibitor.

(3) Guidance of the Specification:

The guidance of the specification as to the prevention of raised blood lipid levels is completely lacking. The specification states on pages 178-180:

“This antihyperlipidemic action is shown for an NHE inhibitor...in the following table, male New Zealand white rabbits (n= 28) having a weight of 3-4kg being used and divided into four groups...” The table provides information detailing that rabbits fed a normal diet and given no drug had overall cholesterol and various subfraction values identical to those of rabbits fed a normal diet and given the drug. Rabbits fed a

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cholesterol diet had substantially higher overall cholesterol and subfraction values. Rabbits fed the cholesterol diet and given the drug had lower overall cholesterol and subfraction values but the values were substantially higher than the control group.

There are no examples showing the complete prevention of raised blood lipid levels.

(4) Working Examples:

Applicant does not provide any working examples for the prevention of raised blood lipid levels.

(5) State/predictability of the Art:

The state of the art regarding treating raised blood lipid levels is relatively high. However, the state of the art for prevention of raised blood lipid levels is underdeveloped.

(6) The Quantity of Experimentation Necessary:

The instant claims read on the prevention of raised blood lipid levels in all of its forms. As discussed above, the specification fails to provide sufficient support for completely preventing raised blood lipid levels. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is

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granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.”

Accordingly the claims are evaluated as a method of treating raised blood lipid levels and not as a method for preventing raised blood lipid levels.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-18 and 20-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Englert et al. (US patent No. 5091394) in view of Robbins Pathologic Basis of Disease (5th ed., pp. 473-476, 519-521, 528-529, and 537-539).

Englert et al. teach, in col. 1 line 5 to col. 2 line 65, benzoylguanidines of formula I (encompassing the presently elected species) as cardioprotective compounds useful in the treatment of arrhythmias and angina pectoris.

Englert et al. do not teach a method of treating or preventing raised blood lipid levels by administration, to a patient in need of such, of a compound of formula I.

Robbins teaches, on page 473, that atherosclerosis is a disease primarily of the elastic arteries consisting of a raised focal plaque within the intima, having a core of lipid (mainly cholesterol and cholesterol esters) and a covering fibrous cap. Robbins teaches, on pages 474-476, that hyperlipidemia (hypercholesterolemia and other abnormalities) is a major risk factor in atherosclerosis. Other major risk factors include hypertension and diabetes. Robbins teaches, on pages 519-521, that there are five mechanisms by which dysfunction of the heart or the overall cardiovascular system can occur: 1) disruption of the continuity of the circulatory system (gunshot wound); 2) disorders of cardiac conduction or arrhythmias; 3) a lesion preventing valve opening or one narrowing the lumen of a vessel which obstructs blood flow; 4) regurgitant flow and 5) failure of the pump itself. On page 521, figure 12-1, the interconnection of hypertension, valvular disease and/or myocardial infarction with hypertrophy and/or

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dilatation and subsequent congestive heart failure, arrhythmias, and/or neuronal stimulation is shown. Robbins teaches, on pages 528-529, that myocardial infarction is the most important form of ischemic heart disease (IHD-also includes angina pectoris) in industrialized countries and that the incidence and major risk factors are the same for atherosclerosis. Thus smoking, hypertension, hypercholesterolemia and diabetes mellitus (and other causes of hyperlipoproteinemia) are the major risk factors in the development of ischemic heart disease and myocardial infarction. Robbins teaches, on pages 537-539, that the consequences and complications of myocardial infarction include cardiac arrhythmias, pulmonary edema, and thromboembolism.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Englert et al. compounds of formula I (encompassing the presently claimed species) in a method of treating or preventing raised blood lipid levels, as the methods of Englert et al. of treating angina pectoris and/or arrhythmias to patients in need thereof would have significant overlap with the patients as presently claimed as Robbins clearly indicates the association of atherosclerosis (and its risk factors of hypertension, diabetes, hypercholesterolemia etc...) with ischemic heart disease (IHD-angina pectoris, myocardial infarction, etc..). Further Robbins clearly indicates that arrhythmias are intimately associated with IHD and can be both a causal factor and a result of IHD. One would be motivated to use the compounds of Englert et al. as they encompass the presently claimed compounds and have already been demonstrated as safe and effective in the treatment of arrhythmias and angina pectoris.

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The examiner respectfully points out the following from MPEP § 2112.01: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Claims 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Englert et al. (US patent No. 5091394) in view of Robbins *Pathologic Basis of Disease* (5th ed., pp. 473-476, 519-521, 528-529, and 537-539) as applied to claims 17-18 and 20-38 above, and further in view of Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (7th ed., pp. 648-649 and 841).

Englert et al. and Robbins are as set forth above.

They do not teach the use of compounds of formula I with ACE inhibitors and/or HMG-CoA inhibitors in the treating or preventing raised lipid blood levels.

Goodman and Gilman's teach, on pages 648-649, that ACE inhibitors are known anti-hypertensive agents. As Robbins has already drawn an association between atherosclerosis and ischemic heart disease with hypertension it is obvious to combine two related treatments with the same goal of reducing the likely hood of the progression of atherosclerosis and IHD.

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Goodman and Gilmans teach, on page 841, that HMG-CoA inhibitors are useful in the lowering of cholesterol in hypercholesterolemic patients.

The examiner respectfully points out the following from MPEP 2144.06:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Conclusion

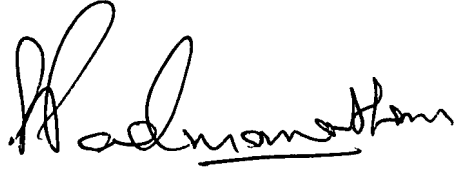
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW



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